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CHATSUDA TUBTIM : STUDY OF ACUTE AND SUBACUTE TOXICITY OF 2,4,6-TRIHYDROXYACETOPHENONE AND ITS EFFECT ON HEPATIC EXCRETORY FUNCTION. THESIS ADVISORS: PRAYAD KOMARATAT, Ph.D., PAWINEE PIYACHATURAWAT, Ph.D., CHAIVAT TOSKULKAO, D.V.M., Ph.D. 167 p. ISBN 974-664-788-1.

Toxicity of phloracetophenone (2,4,6-trihydroxyacetophenone, THA), the aglycone part of phloracetophenone glucoside from *Curcuma comosa* (family Zingiberaceae), which has previously been reported to stimulate bile secretion and lower plasma lipids, was evaluated. Acute toxicity of a single dose of THA was studied in mice (weanlings and adults), hamsters, and rats of both sexes, by oral and intraperitoneal administration. LD_{50} values were dependent on species, sex of animals and routes of administration, but was not age dependent. THA was practically classified as a non-toxic compound when it was given to rats by an oral route (i.g.). The LD_{50} value in adult male and female rats was higher than 6 g/kg BW. Hamsters and mice appeared to be the more sensitive to THA than rats. LD_{50} value via intraperitoneal (i.p.) route in adult males were 338 and 365 mg/kg BW, respectively. At lethal doses, the animals became excited, with ataxia and hypersensitivity to noise, followed by convulsions and death with respiratory paralysis. Subacute toxicity was studied in adult male mice, by giving a daily sublethal dose of THA (37-300 mg/kg BW, i.g.) for 30 consecutive days. A high dose of THA (150 mg/kg BW) induced marked changes of hepatocytes at periportal area including vacuolization of hepatocyte and nuclear degeneration. In severe cases, the affected area was expanded from the periportal area into the central area. Plasma concentrations of liver enzymes, alanine and aspartate aminotransferases and other biochemical parameters including bilirubin, BUN and hepatic triglyceride content were slightly increased. The content of liver glutathione varied but remained within the normal range. It is suggested that THA, particularly at high dose, partially induced subacute toxicities in mice and probably, those toxic effects can be attributed to THA itself, not its metabolite.

Furthermore, hepatic excretory function, after THA treatment, was evaluated by using the sulfobromophthalein (BSP) clearance method. Plasma disappearance and biliary excretion of an intravenous BSP injection were assessed in bile duct-cannulated controls and 17α-ethinylestradiol (EE)-induced cholestatic rats. A single intraduodenal administration of THA at a dose of 50 or 100 mg/kg BW immediately increased bile flow rate, which peaked at 15 min. The acute increase of bile flow rate by THA enhanced hepatic clearance of BSP and decreased plasma alkaline phosphatase in EE-cholestatic rats to normal levels, but did not affect bilirubin. Prolonged treatment with THA for 5 days increased basal bile flow rate and BSP clearance in EE-cholestatic rats. These results suggest that THA at a biologically active dose had low toxicity and might be safe for further development as a therapeutic agent for a short treatment in some hepatic disorders.